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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,833	12/02/2003	Thomas Nelson	17357.01302US	2811

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EXAMINER	
ROOKE, AGNES BEATA	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,833	NELSON ET AL.	
	Examiner	Art Unit	
	Agnes B. Rooke	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19-21* is/are allowed.

6)☒ Claim(s) *1-17,22-25 and 34-41* is/are rejected.

7)☒ Claim(s) *18, 26-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This final action is in response to the Applicant's reply filed on 11/21/2005.

The amendments to the claims and specification filed on 11/21/2005 have been acknowledged.

Claims 1-41 are pending and are currently under consideration.

This application claims priority to 60/430,476, filed in 12/03/2002.

OBJECTIONS/REJECTIONS WITHDRAWN

1. The Objection to the name of "LDL" is withdrawn since the name is spelled out.

2. The Objection to the Specification is withdrawn since the word "days" has been added.

3. The Rejection of claims 1-33, under 35 USC 112, second paragraph, is withdrawn because the term "solid" lipid core is sufficiently described in the specification.

4. The Rejection of claims 28 and 29, under 35 USC 102(b) is withdrawn as being anticipated by Byun et al. (U.S. 6,245,753) because the reference does not specifically teach cholesterol conjugates with adriamycin or tetracycline.

5. The Rejection of claims 1, 5-9, 1-17, 25, 27, 39, and 41, under 35 USC 102(b) as being anticipated by Westensen et al. is withdrawn because the reference does not teach a "recombinant apolipoprotein" and a solid lipid core.

6. The Rejection of claims 25-29, under 35 USC 102(b) as being anticipated by Versluis et al. is withdrawn because the reference does not specifically teach cholesterol linked to adriamycin and tetracycline through an ester linkage.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-17, 22-24, and 34-41 stand rejected under 35 U.S.C. 102(b) as being anticipated by Versluis et al., Stable Incorporation of a Lipophilic Danorubicin Prodrug into Apolipoprotein E-Exposing Liposomes Induces Uptake of Prodrug via Low-Density Lipoprotein Receptor in Vivo, J. Pharmacol. Exp. Ther., (1999), 289(1), p. 1-7.

Versluis et al. made liposomes comprising a lipophilic derivative of daunorbucin, a chemotherapeutic agent (LAD). Cited at page 3, paragraph 2 of specification. [0009-0010] to page 4 [0012].

At page 2, right column, a mixture of egg yolk phopshatidylcholine (EYPC), ^{3}H-Cholesteryl oleate (^{3}H-CO) and LAD was sonicated to form liposomes. The liposomes were subsequently incubated with ApoE. Therefore, the limitations of the method of producing LDL particles as set forth in Claim 34 is taught by Versluis et al. Claim 35 is also anticipated because the diameter was 29.3 (plus-minus 1.1) nM. See page 3, right column.

It is noted that at [0032] of the specification the artificial LDL particles comprising EYPC, cholesterol oleate, and ApoE3 form solid particles comprising a solid lipid core consisting of cholesterol, cholesterol esters, a random active agent, a middle layer

consisting of the fatty acid chains phosphatidylcholine, and a surface layer consisting of phospholipids head groups and ApoE3. At [00103] EYPC and cholesteryl oleate dissolved in methanol and chloroform and evaporated under inert gas nitrogen at 4°C. In Versluis et al. the mixture of EYPC, ^{3}H-CO, and LAD, the solvent dichloromethane was also evaporated in nitrogen at 4°C. At [00103], the evaporated EYPC and cholesteryl oleate was hydrated using Tris-HCl buffer, at pH 8, containing 0.1M KCl and sonicated for 1 hr at 18 μM output under the natural gas nitrogen. This same procedure is performed by Versluis et al., except the inert gas argon was used. At [00104] the liposomes were incubated with ApoE for 30 minutes at 37°C at 1:10 ratio. This same procedure is performed by Versluis et al. **(Claims 34-37)**.

While liposomes are generally considered to be bilayers, See specification [0054], and the claims are drawn to an outer monolayer of phosphatidylcholine, it appears that the liposome of Versluis et al. comprise an outer PC monolayer because the method of making the liposomes as taught in Versluis et al. is nearly identical to the method taught in Example 2 in the instant specification.

Therefore, Versluis et al. teach an artificial LDL particle comprising an outer phospholipids monolayer comprising at least one apolipoprotein and a solid lipid core containing at least one therapeutic agent **(Claim 1)** wherein the apolipoprotein is ApoE3 **(Claims 2 and 3)**. The outer phospholipids monolayer comprises an oxy sterol (^{3}H-cholesteryl oleate) **(Claim 4)**. The therapeutic agent is danorubicin, a chemotherapeutic agent **(Claims 5-8 and 15-17)**. The phospholipids of the outer

phospholipids monolayer was phosphatidylcholine and the apolipoprotein is ApoE3 **(Claims 6 and 7; and Claims 22-24)**.

The particle size of the liposomes of Versluis et al. is taught at page 3, right column, to be 29.3 (plus-minus 1.1) nM, which is a diameter of between 15 and 50 nM **(Claim 8)** and 20-30 nM **(Claim 9).** At page 2, right column, the density of the liposome of Versluis is 1.016 to 1.040 g/ml, which is between 1 and 1.07 g/ml **(Claim 10)** and 1.02-1.06 g/ml **(Claim 11).**

At page 4, left column, the half-life LAP incorporated into the liposomes was enhanced to about 30 minutes. Therefore, at 2 hours, 6.25% of the particle should remain in the serum **(Claim 12).**

Versluis et al. did not assess brain uptake of the LAD when they assessed the tissue distribution of LAD incorporated into liposomes (See Figure 4, for example). However, because the liposomes of Versluis et al. appear to be the same as the LDL particles claimed, one skilled in the art would surmise that the further characterization of the LAD liposome would inherently show that it was transported across the blood brain barrier **(Claim 13)** and had a 3-fold greater uptake specificity for brain when compared to liver **(Claim 14).**

The kit of **Claims 39-41** are included because the composition was in a container and the instructions for use are not given patentable weight.

Versluis et al. administered the LAD liposomes to rats. See page 3, left column, paragraph 2. Therefore, Versluis et al. teach a method for delivering of a substance comprising administration effective amount of a composition comprising LAD liposomes

and pharmaceutically acceptable carrier **(Claims 36-38).** Transport through the blood brain barrier would be inherent to the administration of the LAD liposome.

Applicants argued that their instant invention is distinguished from Versluis et al. because Versluis et al. teach a liposome with a bilayer and that the instant invention teaches LDL particle with only outer phospholipid monolayer; and that it is common knowledge in the art that liposomes are structures with phospholipids bilayers.

Examiner acknowledges the arguments, but in the instant case, the independent claim 1 states that the LDL particle is comprising an "outer phospholipids monolayer," and as the claim reads on its face it is interpreted that the claimed structure comprises an outer phospholipids monolayer but the structure does not exclude a second layer of phospholipids. The rejection is maintained because claim 1 could comprise a second phospholipids monolayer as taught by Versluis et al. Further, while liposomes are generally considered to be bilayers, the claims in the instant invention are drawn to an outer monolayer of phosphatidylcholine, and the liposome of Versluis et al. comprises an outer PC monolayer, where the method of making liposomes as taught in Versluis et al. is nearly identical to the method taught in Example 2 of the instant specification.

New Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 25 is rejected under 35 U.S.C. 103(a) as being obvious over Versluis et al., Stable Incorporation of a Lipophilic Danorubicin Prodrug into Apolipoprotein E-Exposing Liposomes Induces Uptake of Prodrug via Low-Density Lipoprotein Receptor in Vivo, J. Pharmacol. Exp. Ther., (1999), 289(1), p. 1-7.

The teachings of Versluis are disclosed above, where they do not teach conjugates between cholesterol and adriamycin or tetracycline.

However, Versluis et al. teach that LAD consists of danorubicin (a therapeutic agent) linked to cholesteryl-oleate via tetra-peptide spacer. See page 2, column 1, paragraph 2. Therefore, Versluis et al. teach a conjugate of cholesterol and chemotherapic agent.

Therefore, it would have been obvious to one skilled in the art at the time the invention was made to design a conjugate comprising cholesterol linked to adriamaycin or tetracycline because adriamaycin or tetracycline are therapeutic agents just as danorubicin is, as taught by Versluis et al.

Objections to Claims

Claim 18 is objected to because it depends from rejected claim 16.

Claims 26-30 are objected to because they depend from rejected base claim 25.

Claims 31-33 are objected to because they depend from rejected claims.

Conclusion

Claims 19-21 ale allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Jon Weber can be reached on 571-273-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

AR

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER